Rejections under 35 U.S.C. § 112, first paragraph

Claims 9, 10, 11, 12, and 15 were rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification fails to enable the presently claimed invention. For the following reasons, this rejection is traversed.

As an initial matter, applicants note that the factual and legal bases for the Office's maintenance of the lack of enablement rejection are believed to be erroneous, as has been explained previously (see, for example, applicants' Preliminary Amendment mailed on June 6, 2000). The points made in that Amendment are expanded on below, and the Office's newly stated grounds for maintaining this rejection are addressed as well.

The enablement rejection, as applied to claims 9 and 10, focuses on whether applicants' methods are efficacious for treating AIDS using *in vivo* or *ex vivo* gene therapy. In essence, the Office asserts that applicants failed to provide an enabling description of their therapeutic method because they failed to teach delivery of the disclosed vector, SeVSDF-1α, to any cell type *in vivo*. This basis of the enablement rejection is unfounded.

As an initial matter, applicants again point out that their specification plainly teaches *in vivo* and *ex vivo* gene therapy methods. As evidence of this assertion, applicants direct the Office's attention to their specification, for example, at page 8 (lines 32-36), where it is stated:

> The nondisseminative recombinant Sendai virus vector of the present invention can be used for gene therapy *ex vivo* or *in vivo*. The *ex vivo* method can be performed by collecting target cells from human subjects, infecting the cells with rSev, and giving the infected cells back to the human subjects.

The specification, for example, at page 8 (lines 36-37), also teaches adminstration of such viral vectors directly to a patient:

> The *in vivo* method can be performed by administering the virus vector to human subjects.

At page 9 (lines 1-4), the specification teaches viral dosages useful to practice the claimed methods:

> The dose of the virus vector varies depending on the age, weight, and symptoms of the patients, the administration route, and the kinds of chemokines. The virus vector is administered at 0.1 to 10,000 virions/cell, preferably 0.5 to 50 virions/cell.

Furthermore, the specification, at page 8 (lines 23-31), teaches pharmaceutical formulations useful in the invention.

In view of this teaching, applicants' specification provides ample guidance for a person of ordinary skill in the art of gene therapy to carry out an *in vivo* gene therapy procedure according to the present invention. A gene therapy vector is provided by applicants, as are dosage and pharmaceutical carrier formulations. Moreover, applicants provide ample instructions for expressing a biologically-active chemokine in mammalian cells using a gene therapy vector of the invention.

In addition, to substantiate the fact that Sendai virus vectors are indeed efficacious for *in vivo* and *ex vivo* gene therapy, the Office's attention is directed to the accompanying paper by Yonemitsu et al. (*Nature Biotechnology* 18: 970-973, 2000) entitled "Efficient gene transfer to airway epithelium using recombinant Sendai virus," on which co-inventor, Yoshiyuki Nagai, is a co-author. In this publication, experimental results are presented demonstrating that a recombinant <u>Sendai virus vector</u> can be

administered for efficacious gene transfer *in vivo*. Here, Yonemitsu demonstrated that recombinant Sendai virus vectors efficiently transfect cells of the respiratory tract of both mice and ferrets *in vivo*, as well as freshly obtained human nasal epithelium cells *in vitro*. These results clearly substantiate the teachings of applicants' specification; namely, that a recombinant Sendai virus expression vector is useful for either *in vivo* or *ex vivo* gene therapy or both.

Moreover, applicants direct the Office's attention to the accompanying declaration of Dr. Yasuji Ueda, a research scientist at DNAVEC Research Inc., the assignee of the above-referenced application. There, Dr. Ueda describes experiments demonstrating that recombinant Sendai virus vectors have been used to successfully infect human myeloid CD34 positive cells. Moreover, Dr. Ueda attests to the fact that a recombinant Sendai virus vector can transfer genes into human CD34 positive cells with a gene transfer efficiency ranging from about 40% to 70%. These findings, like those described by Yonemitsu, provide further evidence that applicants' specification broadly enables the full scope of the present claims directed to using Sendai viral vectors for *in vivo* or *ex vivo* gene therapy.

The Office further asserts that applicants' specification lacks enablement because its teaching is inadequate with respect to the appropriate dose per route of administration. The Office states:

> The dose per route of administration for use with the claimed invention is undetermined, and cannot be easily assessed by the skilled artisan because the specification does not disclose measurements on the use of the claimed vector with any cell type which would realistically be transfected *in vivo*, or even used for *ex vivo* gene therapy. To utilize the claimed invention for gene therapy, the artisan

> would still be required to practice undue experimentation to determine the amount of SDF-1α expressed from each cell type, and the appropriate modifications which may be required to increase the level of expression such that therapeutic benefit in the treatment of HIV would occur for gene therapy.

These grounds for the rejection are respectfully traversed.

Applicants note that ordinarily skilled medical practitioners are capable of determining the appropriate dosage of therapeutic Sendai virus vectors or cells harboring such vectors for administration in this context. Applicants further note that this type of determination is ultimately made in standard FDA clinical trials. Indeed, testing for dosage effectiveness is required for obtaining government approval to market a therapy for human use, not to obtain a patent. *See Scott v. Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d 1115 (Fed. Cir. 1994) ("Testing for full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.") Furthermore, even if there were a diminution of expression, that would not necessarily eliminate the therapeutic benefit of the invention.

Applicants also point out that, to satisfy the enablement requirement of § 112, one need only demonstrate pharmacological activity *in vitro*. This is stated clearly in *In re Brana*, 51 F.3d 1562 (Fed. Cir. 1995), where Judge Plager stated:

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many areas.

> In view of all of the foregoing, we conclude that applicants' disclosure complies with the requirements of 35 U.S.C. § 112, first paragraph.

In this case, applicants, in their specification, have plainly demonstrated that a recombinant chemokine, encoded on a Sendai virus vector, had anti-HIV activity *in vitro*. As direct evidence of this point, applicants direct the Office's attention to the specification, for example, at pages 10-14, where it was demonstrated that not only were substantial amounts of the chemokine, SDF-1α, produced in a chicken embryo fibroblast host cell using the disclosed recombinant Sendai virus expression vector system (see, Example 2, pages 10-11), but also that this chemokine had anti-HIV activity (see, Example 4, pages 11-14). Here applicants demonstrated that recombinant SDF-1α suppressed the replication of three different T cell line tropic HIV-1 strains: NL43, SF33, and TK11, in the MT4 cell line, and one syncytium inducing primary isolate (page, 13, lines 21-23). This evidence clearly demonstrates the workability of the claimed invention for both *in vivo* and *ex vivo* gene therapy situations.

The PTO's MPEP is equally clear that it is not necessary to demonstrate *in vivo* activity to satisfy the enablement requirement (MPEP § 2107.02):

> The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a <u>reasonable correlation</u> between the activity and the asserted use (emphasis added). *Nelson v. Bowler*, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980).

The Office may not disregard the clear direction of *Brana* and the MPEP with citations to articles found in the literature where a cited reference does not in fact describe an

experiment in which the claimed treatment failed. In this case, Crystal, Miller, Deonarian, and Verma, contain absolutely no description of any experiment in which a recombinant Sendai virus vector was utilized to effect gene therapy either *in vivo* or *ex vivo*. Thus, because these cited references do not even mention the methods of the claimed invention, the references cannot be interpreted as affecting the patentability of the present claims. The guidelines in case law, instructing that *in vitro* evidence is adequate, should be followed.

Finally, the Office Action states:

> It has also been determined that the specification fails to provide an enabling disclosure for a method of conducting protein therapy (claim 15) because the specification is void of methods of administering a recombinantly derived SDF-1 to a subject to include dosing regime and route of administration such that any therapeutically effective treatment of HIV would be expected to occur. Lastly, in light of the fact the specification fails to provide an enabling disclosure for the use of any method of treatment in a human subject (e.g., claims 9, 10, 15), then it has also been determined that the specification is not enabling for a composition with an intended use as a pharmaceutical.

To address this basis of the enablement rejection, applicants again direct the Office's attention to their *in vitro* results demonstrating the production of a biologically-active chemokine having anti-HIV activity. Again, as is stated above, applicants' *in vitro* evidence is adequate. Furthermore, ordinarily skilled medical practitioners are readily capable of determining the appropriate dosage of a therapeutic chemokine for administration to a human in this context, as well as determining the appropriate administrative route. Moreover, as is noted above, this type of determination is ultimately made in standard FDA clinical trials.

Rejections under 35 U.S.C. § 102(a)

Claims 1-8, 11, 12, 14, and 15 were rejected under 35 U.S.C. § 102(a), as being anticipated by Moriya *et al.* (*FEBS Letters* 125: 105-111, 1998). This rejection is respectfully traversed.

The Moriya reference is not prior art to the present invention. This reference was published in 1998, less than a year before the August 11, 1998 filing date of the present application. Applicants are the joint inventors of the pending claims and are the joint contributors of any relevant information in the Moriya reference, notwithstanding the inclusion of the additional authors, and a Declaration of Yoshiyuki Nagai, a co-inventor of this application, to this effect is attached. Accordingly, the Moriya reference does not constitute prior art in this application (*In re Katz*, 687 F.2d 450 (C.C.P.A. 1982)), and the § 102(a) rejection may be withdrawn.

Rejections under 35 U.S.C. § 103 (a)

Claims 1-8, 11, 12, 14, and 15 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Yu *et al.* (*Genes to Cells* 2: 457-466, 1997) in view of Bleul *et al.* (*Nature* 382: 829-832, 1996). This rejection is based on the assertion that:

> In light of Yu and Bleul et al, it would have been obvious to one of ordinary skill in the art to use the SeV vector disclosed by Yu to express SDF-1 in vitro. One would have been motivated to do this to yield high volume of biologically-active SDF-1 which could then be used for protein therapy in the treatment of HIV.

Applicants respectfully disagree.

Applicants' claimed invention is generally directed to a recombinant Sendai virus vector expressing a biologically-active chemokine (claims 1-5). In addition, claims 6-8 are directed to a method of producing a biologically-active chemokine using a recombinant Sendai virus vector. The invention is further directed to a pharmaceutical composition including a recombinant Sendai virus vector expressing stromal cell-derived factor α or β, where the vector is either disseminative (claim 11) or infectious and replicates autonomously, but is not disseminative (claim 12). Claim 14 is directed to a host cell that is transfected with a recombinant Sendai virus vector that expresses a chemokine. And claim 15 is directed to a method of inhibiting HIV proliferation which includes, incubating a host cell transfected with a recombinant Sendai virus vector that expresses a chemokine *in vitro* to allow secretion of a substantial amount of biologically-active chemokine; and contacting the chemokine with cells that are infected with HIV. Because neither Yu (1997) nor Bleul disclose any aspect of applicants' invention, these references cannot render the claimed invention obvious.

To support the obviousness rejection, the Office cites Yu (1997) for the proposition that a Sendai virus vector has been used for the successful expression of HIV-1 gp120 in mammalian cells. In addition, the Office dismisses Yu's failure to express biologically-active luciferase as an inherent characteristic of the molecule. As is discussed below, the Office cannot ignore Yu's failure to produce functional luciferase.

With respect to Yu's failure to produce biologically-active luciferase, the Office maintains that "[i]t is a characteristic of the luciferase protein that it aggregates and

becomes biologically inactive, and not due to the vector itself." Applicants respectfully disagree with this generalization.

As an initial matter, applicants direct the Office's attention to the accompanying publications by DeWet et al. (*Molecular and Cellular Biology* 7: 725-737, 1987) entitled "Firefly Luciferase Gene: Structure and Expression in Mammalian Cells" and Yu et al. (*Molecular and Cellular Biology* 15: 4867-4872, 1995) entitled "Virus-Mediated Expression of Firefly Luciferase in the Parasitic Protozoan *Giardia lamblia*." In DeWet, the successful expression of functional luciferase in a mammalian cell is demonstrated. See for example, DeWet, at page 730, right panel, paragraph two. Similarly, Yu (1995) demonstrated the successful expression of functional luciferase in a protozoan. See, for example, Yu (1995) at page 4869, right panel, paragraph two. Furthermore, applicants note that aggregation is not merely a chemical property of the luciferase molecule itself since factors such as temperature, protein concentration, and denaturant concentration have been described to affect luciferase aggregation. As evidence of this assertion, the Office's attention is directed to Figure 3 of the accompanying publication by Herbst et al. (*Biochemistry* 37: 6586-6597, 1998) entitled " Folding of Firefly (*Photinus pyralis*) Luciferase: Aggregation and Reactivation of Unfolding Intermediates," which describes the influence of temperature and protein and denaturant concentrations on luciferase aggregation. Given such evidence, the Office's contention that luciferase aggregation is an inherent property of the molecule is unavailing.

Applicants also note that, like luciferase, chemokines were also notorious for self-aggregation leading to biological inactivity of the molecule. Indeed, given the many

failures in the art for expressing a biologically-active chemokine, the use of a Sendai virus vector expression system to express a biologically-active chemokine was not readily apparent. Chemokines, for example, have not only been found to aggregate in eukaryotic expression systems, but have also been shown to aggregate when expressed in prokaryotes. As is stated in the specification on page 2, lines 19-21 and lines 24-25, the expression of basic chemokines has not been successful in *E. coli* due to aggregation. Given the repeated failure to produce non-aggregated basic chemokines using a variety of expression systems, one skilled in the art would hardly be motivated to use the claimed Sendai virus vector expression system in an attempt to express a biologically-active product. Thus, selecting a Sendai virus expression vector for expressing a biologically-active chemokine, from a myriad of expression vectors available in the art, simply was not readily apparent in view of the art's repeated failures.

Applicants also note that Yu's (1997) successful expression of HIV-1 gp120 using a Sendai virus vector does not extrapolate to the successful expression of an unrelated, biologically distinct protein such as a chemokine. This is because the expression of HIV gp120 using a Sendai virus vector does not predict expression of an exogenous chemokine using that expression system. As evidence of this assertion, applicants direct the Office's attention to the accompanying Declaration of Dr. Makoto Inoue, a research scientist at DNAVEC Research Inc., the assignee of the above-referenced application. As noted by Dr. Inoue, the production efficiency of two proteins, nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF) was examined in the recombinant Sendai virus expression system. Using such an expression system, Dr.

Inoue attests that NGF was produced 60,000 to 80,000 times better than GDNF. Moreover, Dr. Inoue attests that expression of a foreign gene does not affect the replication of the Sendai virus. Indeed, Dr. Inoue concludes that exogenous proteins encoded by the recombinant Sendai virus can be made at vastly different levels and that the influence of the exogenous gene on the production efficiency of proteins, when using any given viral vector-protein combination, cannot be predicted. Accordingly, it is entirely unreasonable to extrapolate results obtained for the expression of HIV-1 gp120 to predict the expression of any protein, including the expression of a biologically-active chemokine. Thus, predicating successful expression of a chemokine based on the production of HIV-1 gp120 is an "apples and oranges" comparison that is entirely inappropriate.

With respect to Bleul, this reference neither discloses nor suggests the use of a Sendai virus vector to express a biologically-active chemokine. Indeed, Bleul was satisfied using a synthetic chemokine for his experiments. It is well-established in patent law that obviousness cannot be established by combining references to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under § 103(a), teachings of references can be combined <u>only</u> if there is some suggestion or incentive to do so. Clearly, since Bleul and Yu, either alone or in combination, fall far short of teaching a protocol for expressing a biologically-active chemokine using a Sendai virus vector expression system, both the suggestion and the incentive to produce biologically-active chemokines using such an expression system are absent.

Finally, the fact that the inventors succeeded in expressing a biologically-active chemokine has significant clinical implications for treating human immunodeficiency virus. On this point, the Office's attention is directed to the accompanying publication by Czaplewski et al. (*Journal of Biological Chemistry*: 274: 16077-16084, 1999) entitled "Identification of Amino Acid Residues Critical for Aggregation of Human CC Chemokines Macrophage Inflammatory Protein (MIP)-1α, MIP-1β, and RANTES." By studying aggregated and disaggregated forms of human CC chemokines, Czaplewski found that disaggregated chemokines retained their HIV inhibitory activity. Moreover, Czaplewski concluded that disaggregated chemokines are necessary for safe clinical investigation. See, for example, Czaplewski's abstract at page 16077. Thus, applicants' successful production of a biologically-active chemokine represents a significant advance in the medical community.

Secondary Considerations

Over and above everything that was said above is the fact that there are in this case compelling objective indicia of nonobviousness. As is discussed above and as previously indicated, the instant invention succeeded where other had failed. The Office must give weight to such important secondary consideration; *In re Sernaker*, 702 F.2d 989, 217 U.S.P.Q. 1 (Fed. Cir. 1983).

In sum, the references of record do not indicate that the claimed Sendai virus vector is a useful expression system for expressing a biologically-active chemokine. There is nothing in any of the references to suggest or even predict that the claimed invention would be successful, and, in fact, at least one of the references, Yu (1997), in

teaching the production of non-functional, aggregated luciferase, teaches away from the invention. In short, the references do not convey to those of ordinary skill a reasonable expectation of success in producing biologically-active chemokines using a Sendai virus vector expression system. Accordingly, it is respectfully submitted that the § 103(a) rejection of claims 1-8, 11, 12, 14, and 15 should be withdrawn.

CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is respectfully requested.

Enclosed is a petition to extend the period for replying for three months, to and including March 12, 2001. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 12 March 2001

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